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Abstract

Objective We evaluated rates of all-cause mortality and self-harm in association with clozapine treatment in individuals with treatment-resistant schizophrenia. **Method** A population-based cohort of 2,370 individuals with treatment-resistant schizophrenia after Jan 1, 1996 was followed until death, first episode of self-harm, emigration, or June 1, 2013. Time to all-cause death and time to first episode of self-harm was analyzed in Cox regression models with time-varying treatment, adjusted for clinical and sociodemographic covariates. **Results** The rate of all-cause mortality was higher for no clozapine compared with clozapine treatment, HR = 1.88 (95% CI: 1.16 – 3.05). This was mainly driven by periods of no antipsychotic treatment, HR = 2.50 (1.50 – 4.17), with non-significantly higher mortality on other antipsychotics, HR = 1.45 (0.86 – 2.54). An excess mortality was observed in the year after clozapine discontinuation, HR = 2.65 (1.47 – 4.78). The rate of self-harm was increased for non-clozapine antipsychotic treatment compared with clozapine, HR = 1.36 (1.04 – 1.78). **Conclusions** Our results demonstrated a nearly two-fold higher mortality among individuals with treatment-resistant schizophrenia not being treated with clozapine compared with clozapine-treated individuals. Furthermore, our results suggest a harmful effect of other antipsychotics regarding self-harm compared with clozapine. It remains to be investigated to what extent the observed excess mortality after clozapine discontinuation is confounded by non-adherence and other unobserved factors and to what extent it is mediated by adverse effects from recent clozapine exposure or deterioration in physical or mental health precipitated by clozapine discontinuation.

Key words: treatment resistance, all-cause mortality, schizophrenia, discontinuation, antipsychotics

Introduction

Clozapine is the most effective antipsychotic treatment for treatment-resistant schizophrenia (TRS) (1), and is recommended for such patients in Danish and several other national guidelines (2-4). However, clozapine is underused in most countries, probably due to the fear of severe side effects and the inconvenience of therapeutic blood monitoring (5). Consequently, alternative treatment strategies such as switching or augmenting with other antipsychotics are often applied (6). Antipsychotic polypharmacy is – despite the lack of evidence for its efficacy – commonly prescribed (7).

An excess early mortality in schizophrenia has been demonstrated in several studies, with elevations in rates of both natural and unnatural causes of death (8, 9). Mortality in association with antipsychotic treatment – especially clozapine – has been studied extensively over the past decades. The *FIN11-study* found a significantly lower mortality among users of clozapine compared with users of any other antipsychotic drugs (10). Several studies similarly concluded that clozapine was associated with a lower all-cause mortality compared with no antipsychotics or first-generation antipsychotics (11), never clozapine users (12), and past or recent clozapine use (13). Other studies did not find significant differences in all-cause mortality between clozapine and haloperidol (14) or other antipsychotics (15). Clozapine has particularly been found to be associated with a lower risk of suicide (10, 11, 14) and suicide attempts (14, 16). However, concern about a potentially higher risk of suicide following clozapine discontinuation has been raised (17).

These studies are comparable in their use of an observational design, which is required because randomized controlled trials cannot address the issue of mortality in association with clozapine due to the unfeasibly large sample size and long follow-up time that would be required to detect differences in a relatively rare outcome. However, observational studies differ in length of follow-up, model adjustment, and exposure definition used. Moreover, most previous observational studies used different comparison groups, including individuals with schizophrenia or schizophrenia spectrum disorders not eligible for clozapine, leading to the problem of confounding by indication: it was not possible to distinguish whether the effect on mortality was due to clozapine treatment, specifically, or to treatment-resistant schizophrenia in general. One exception is the study by Stroup and colleagues (15), which restricted the study cohort to treatment resistant individuals and found no significant difference in all-cause mortality and self-injurious behavior when comparing clozapine users with individuals using other antipsychotics (15). Even though a potentially adequate comparison group was selected, follow-up was restricted to one year, and mortality after clozapine discontinuation was not studied. Another study examined mortality in current or past clozapine users, but did not include individuals eligible but not receiving clozapine (13).

The aim of the present study was to evaluate rates of all-cause (and cause-specific) mortality and self-harm in association with clozapine treatment and alternative antipsychotic treatment strategies, among individuals with schizophrenia meeting criteria for treatment resistance.

Method

Data sources

We extracted information on medication from The Danish National Prescription Registry, where all outpatient drug prescriptions have been registered since 1995 (18). We obtained information on admission dates and diagnoses (WHO International Classification of Diseases (ICD) version 8 and 10) from the Danish Psychiatric Central Research Register and the Danish National Patient Registry (19, 20). We obtained information on sex, date of birth, vital status, and nationality and parents' personal identification numbers from the Danish Civil Registration System(21). Information on causes of death was obtained from the Causes of Death Register with information available until December 31, 2011 (22). The unique personal identification number was used to link individual data across the national registration systems, including registers holding socio-demographic information (21).

Study cohort

We conducted a population-based cohort study. The cohort comprised all individuals born in Denmark after January 1, 1955 with a first diagnosis of schizophrenia (ICD 8: 295.x9, excl. 295.79; ICD-10: F20) at age 18 or older after January 1, 1996 and fulfilling criteria for treatment resistance before June 1, 2013. To define the cohort and start of follow-up (baseline), we used a register-based definition of treatment-resistant schizophrenia based on either of the following two criteria: (i) clozapine prescription redeemed from the pharmacy, or (ii) psychiatric hospital admission within 18 months during continued treatment with antipsychotics after at least two periods of different antipsychotic monotherapy, each lasting at least 6 weeks. The definition has been applied and described more fully elsewhere (23).

Mortality and self-harm

We studied all-cause and cause-specific mortality as well as first recorded episode of self-harm after meeting criteria for treatment resistance. All-cause mortality was defined using the recorded date of death retrieved from the Danish Civil Registration System, where the vital status is continuously updated. We assessed causes of death from the Causes of Death Register: suicide, death from diseases and medical conditions, death from other external causes, as classified in a previous study (24). Self-harm was defined as the first registered episode of self-harm after meeting criteria of treatment resistance. Self-harms included suicide attempts as

well as self-harm such as cutting and poisoning (excl. food, alcohol, and mild analgesics) (25-28).

Clozapine and other antipsychotic treatment

The primary exposure was defined as time-varying treatment, classifying individual follow-up time into periods of clozapine treatment and no clozapine treatment. This was defined from prescription data as described in Supplementary Table 1. No clozapine treatment was further classified into non-clozapine antipsychotic treatment and no antipsychotic treatment such that the former could serve as an active comparator group.

Secondary exposure measures were defined. First, to account for periods of concomitant antipsychotic treatment, treatment status was classified into the following sub-categories: clozapine monotherapy (reference), clozapine with other antipsychotics, non-clozapine antipsychotic polypharmacy, non-clozapine antipsychotic monotherapy, and no antipsychotic treatment. Next, to study the timing of all-cause mortality in relation to clozapine, the time-varying treatment was classified as periods of past, no, and current clozapine treatment.

Potential confounders

We adjusted for sex and previous episodes of self-harm as well as the following time-dependent factors: age; calendar year; comorbid substance abuse; comorbid somatic disorders (Charlson index score > 0) (29); comorbid psychiatric diagnoses: other schizophrenia spectrum disorders, singular or recurrent depression, personality disorder; living in the capital area; and cumulative clozapine treatment (0, 0-1, 1-3, 3+ years).

Data analysis

We performed crude and adjusted Cox proportional hazards regression and analyzed time to death as well as time to the first recorded episode of self-harm in separate models, where individuals were followed from the date of meeting criteria (i) or (ii), whichever came first. Individuals were censored at emigration from Denmark or end of follow-up (June 1, 2013). Clozapine treatment (the recommended treatment in treatment-resistant schizophrenia) was used as the reference, allowing for direct presentation of hazard ratios (HRs) for several comparisons including different antipsychotic treatment strategies. This implies that, e.g. an HR above 1 favors clozapine as it has a lower event rate. Estimates for the opposite comparison can easily be obtained by inversion of both HR and confidence limits. For all-cause mortality, we additionally studied the timing of death by comparing rates after clozapine discontinuation (designated as past clozapine treatment) and rates during non-clozapine-exposed treatment with rates during current clozapine treatment. For this analysis, we reset the time period at the beginning or end of a clozapine treatment period. Because individuals could contribute to several treatment periods, we used robust standard errors to account for intra-individual

correlation. HRs were presented for models splitting follow-up into the following time intervals: 0-1, 1-3 and 3+ years to assess the timing of death after clozapine discontinuation. For cause-specific death, analyses were conducted for crude and partly adjusted models and with further adjustment for psychiatric hospitalization the previous year. Individuals were censored at death from other causes, emigration from Denmark, or last available information on cause of death from the Causes of Death Register (December 31, 2011).

The proportional hazards assumption for the Cox regression models was evaluated from diagnostic plots for baseline variables. All estimates are accompanied by 95% confidence intervals (CIs). All analyses were conducted in Stata version 13.

Sensitivity analyses

First, we repeated the analyses with exclusion of inpatient stays at psychiatric hospitals lasting longer than one month to account for the fact that we do not have information on medication during hospitalization. Next, an analysis was conducted, censoring at first change in treatment status (i.e. only following individuals until their first discontinuation of initial clozapine or other antipsychotic treatment). The main analyses were repeated with long-acting injectable antipsychotics in a separate category, adjusted for a smaller set of potential confounders due to fewer events in one category. Another approach – a so-called initial-treatment approach – was applied, where treatment status was obtained at baseline and was carried forward during the entire follow-up period. Analyses were conducted based on multivariable models as well as based on a propensity score-matched cohort adjusted for a large set of potential confounders (Supplementary Table 3). A description of the method can be found in the Supplementary material.

Results

Baseline characteristics in relation to exposure and outcome

We identified 2370 individuals meeting criteria for treatment-resistant schizophrenia. 45.8% were women (Table 1), and the median age at the point of meeting criteria for treatment resistance was 30.1 years (inter-quartile range (IQR): 24.8 – 37.3). In total, 158 (6.7%) died, and 602 (25.4%) had at least one episode of self-harm registered during follow-up (maximum of 17 years, median=6.8 years, IQR: 3.2 – 10.6). The overall rates per 100 person-years were 0.9 (95% CI: 0.8 – 1.1) for all-cause death and 4.6 (95% CI: 4.2 – 5.0) for self-harm. Rates of death, as well as rates of self-harm, differed across most baseline characteristics (Table 1). 1372 individuals (58%) with treatment-resistant schizophrenia initiated clozapine during follow-up. Among these, the median number of clozapine treatment periods was 3, and the median duration of a single clozapine treatment period was 10 months (IQR: 5 – 19 months). Clozapine users were

younger and more likely to have been admitted to a psychiatric hospital within the previous year, but were less likely to have had a diagnosis of substance abuse and to have lived in the capital area (Table 1).

[Table 1 approximately here]

Dividing follow-up into different kinds of treatment status, the distribution of risk time was: clozapine monotherapy (15%), clozapine with other antipsychotic (17%), non-clozapine antipsychotic monotherapy (26%), other antipsychotic polypharmacy (16%), and no antipsychotic treatment (26%) throughout follow-up.

All-cause mortality and clozapine

In a Cox regression model with time-varying clozapine treatment, we found that no clozapine treatment was associated with an elevated rate of all-cause mortality, HR = 1.88 (1.16 – 3.05), compared with clozapine treatment in adjusted models. Estimates were substantially higher for no antipsychotic treatment, HR = 2.50 (1.50 – 4.17), and somewhat higher for non-clozapine antipsychotic treatment, HR = 1.45 (0.86 – 2.45), compared with clozapine treatment (Table 2, Model B). When comparing different treatment strategies with clozapine monotherapy, again no antipsychotic treatment was associated with the highest rate of death compared with clozapine treatment, HR = 2.66 (1.36 – 5.18), whereas no significant differences were seen when comparing clozapine monotherapy with any other antipsychotic treatment strategy. The HR estimate comparing non-clozapine antipsychotic monotherapy with clozapine monotherapy was high, although insignificant, HR = 1.75 (0.87 – 3.50) (Table 2, Model B).

[Table 2 approximately here]

Rates of all-cause mortality were highest after clozapine discontinuation, particularly within the first year after clozapine discontinuation when compared with rates during clozapine treatment (Figure 1). Compared with current clozapine treatment, the one-year mortality hazard ratios adjusted for sex, age, calendar year, psychiatric hospitalization, and comorbid somatic diseases were 1.35 (0.61 – 2.97) in periods of no past or current clozapine treatment and 2.68 (1.49 – 4.82) in periods after clozapine discontinuation.

[Figure 1 approximately here]

Cause-specific mortality and clozapine

The analyses with cause-specific mortality included 2141 individuals, of whom 125 (5.8%) died during follow-up. The estimated adjusted HRs for non-clozapine antipsychotic treatment or no antipsychotic-based treatment at all were (clozapine treatment as reference): 1.74 (0.59 – 5.12) for suicide; 1.41 (0.80 – 2.49) for other external causes of death; and 0.77 (0.31 – 1.89) for deaths from other diseases or medical conditions (Table 3, Model C).

[Table 3 approximately here]

Self-harm and clozapine

Non-clozapine antipsychotic treatment was associated with an elevated rate of self-harm, HR = 1.36 (1.04 – 1.78), compared with clozapine treatment in adjusted models, whereas no association was found when comparing no antipsychotic treatment with clozapine treatment HR = 1.15 (0.86 – 1.53) (Table 4, Model B). Estimated rates of self-harm were lowest for clozapine (monotherapy or polypharmacy) and highest for non-clozapine antipsychotic polypharmacy, but no significant differences were found across treatment strategies in any of the models (Table 4).

[Table 4 approximately here]

Influence of sensitivity analyses

When excluding periods of psychiatric hospitalization lasting longer than one month, effect sizes were slightly decreased in most comparisons, but the conclusion was unaltered in all models (Table 2 and Table 4). The analyses censoring at first change in treatment status resulted in substantially increased HRs of 3.58 (1.14-11.27) for all-cause mortality (crude analysis due to few events), and an adjusted HR of 3.08 (1.25-7.57) for self-harm. Analyses of long-acting injectable antipsychotics compared with clozapine resulted in adjusted HR=1.28 for all-cause mortality and adjusted HR=1.24 (0.99-1.79) for self-harm (Supplementary table 2). Presentation of results of the initial-treatment approach are shown in the supplementary material (Supplementary tables 3 and 4).

Discussion

This study demonstrated that clozapine treatment in treatment-resistant schizophrenia was associated with a substantially lower rate of all-cause mortality compared with no antipsychotic treatment, with an increase in mortality after clozapine discontinuation. Moreover, we found a significantly lower rate of self-harm during clozapine treatment compared with non-clozapine antipsychotic treatment in treatment-resistant schizophrenia, regardless of the statistical model or exposure stratification used.

Our findings of a lower mortality in association with clozapine are in line with findings of previous studies (10-12). Our results indicate a potential protective effect of clozapine when compared with other antipsychotics, particularly non-clozapine antipsychotic monotherapy in treatment-resistant schizophrenia, but results were not statistically significant. Whereas some studies have not been able to detect a significant protective effect of clozapine compared with other antipsychotics (14, 15), other studies have demonstrated a significantly lower risk of overall death or suicide in clozapine users, even when compared to other second-generation

antipsychotics (10, 11). The estimated effects of current clozapine treatment compared with other antipsychotics in the present study were, although statistically insignificant, of fairly similar size as the effect estimates of clozapine compared with perphenazine observed in the FIN11-study (10).

Our findings of significantly reduced rate of self-harm in clozapine users corroborate previous research (14, 16). Unexpectedly, no significant effect was observed in adjusted analyses when comparing clozapine with no antipsychotic treatment, and the highest rate of self-harm was observed for non-clozapine antipsychotic polypharmacy. More evidence is needed to further explore whether alternative antipsychotic treatment strategies to clozapine in treatment-resistant schizophrenia might increase the risk of self-harm, even when compared with no antipsychotic use.

The study by Stroup and colleagues was likely closest in design to our study in that they also restricted the cohort to treatment-resistant schizophrenia, although they restricted to one year of follow-up (15). Unlike their study, with no significant findings of reduced all-cause mortality and self-injurious behaviour in clozapine users compared with other antipsychotic users, we found a reduced rate of mortality and self-harm associated with clozapine treatment. However, when we restricted to one-year follow-up or first change in treatment status, even larger effect sizes were observed than in analyses based on the entire follow-up period. Differences in findings between the studies might to some extent be explained by differences in exposure and outcome definitions used, unmeasured confounding, and different treatment settings.

In line with previous research (10, 13, 14), we found the largest effect size for suicide. In the present study, lower estimates for death caused by medical conditions during clozapine treatment also indicate a protective effect of clozapine. For analyses of cause-specific mortality, the number of events was small, and a potential statistically significant association could not be detected.

In the present study, we found that mortality was increased after discontinued clozapine treatment with a significant excess mortality in the first year, or even within three months after discontinuation, in line with what has been found previously (13). This indicates that death after clozapine discontinuation, probably caused by other causes than suicide, is a cause for concern (17). We do not know whether the severity of disease (mental or somatic) caused the discontinuation or the other way around. One potential explanation is that clozapine, or at least redemptions from the pharmacy, are discontinued because of severe medical conditions related or unrelated to treatment with clozapine, also known as the 'sick-stopper effect' (30). Side effects and deaths have been reported as the most common reasons for discontinuation (31). One study found that adverse drug reactions accounted for over half of clozapine

discontinuations, with sedation being the clearly most common, followed by neutropenia and tachycardia (32). In the present study, the number of deaths within the year following clozapine discontinuation was not sufficient to stratify analyses by different causes of death.

The present study was the first to study mortality and self-harm across different treatment strategies in comparison with clozapine in a cohort of individuals with apparent treatment-resistant schizophrenia. Mortality rates were highest in periods of no antipsychotic treatment and significantly lower in periods of clozapine treatment. Rates of episodes of self-harm were highest in periods of non-clozapine antipsychotic treatment and significantly lower in periods of clozapine treatment. Adjusted analyses with long-acting injectable antipsychotics in a separate category indicated that the increased rate of self-harm was particularly driven by other antipsychotics. The reductions in mortality or self-harm comparing different antipsychotic treatment strategies with clozapine monotherapy did not reach statistical significance, probably due to fewer events in each exposure category.

Strengths and limitations

A major strength of the present study is the population-based, longitudinal study design linking several registers to gather information obtained at baseline as well as time-varyingly over a long period of up to 17 years of follow-up. All medication redeemed at all pharmacies in Denmark since 1995 was available, and the fact that the individual redeemed the medication from the pharmacy largely takes care of adherence. Another strength of the study is the restriction to a cohort of individuals meeting criteria for treatment resistance, which we consider the most appropriate approach for studying outcomes in relation to clozapine treatment, because all members of the cohort are considered to have an indication for clozapine. The study population used by Stroup and colleagues was also restricted to individuals with treatment-resistant schizophrenia (15), but unlike them we additionally used a time-varying treatment design which enabled us to study the temporal and acute treatment effects over long-term follow-up, adjusting for several time-dependent factors associated with treatment and outcome. As a consequence of our chosen design we assigned periods of no antipsychotic prescriptions to a separate exposure category.

Observational studies using registry data have some limitations. One limitation is the lack of information on antipsychotic medication status during hospitalization. However, we repeated analyses excluding periods of psychiatric hospitalization exceeding one month, resulting in similar estimates. Also, for a minor proportion of individuals, antipsychotic medication has been dispensed up to 2 years free of charge through hospital pharmacies since 2008, resulting in no antipsychotic prescriptions being visible for these individuals during this period. This might have biased the estimates, but by restricting follow-up to 2007, analyses resulted in similar estimated effect sizes.

The current study compared clozapine treatment with different overall treatment strategies, but not with specific antipsychotic drugs such as the FIN-11 study (10). However, the current study is to our knowledge the first study to compare clozapine with other antipsychotic monotherapy and long-acting injectable antipsychotics in treatment-resistant schizophrenia.

The outcome in the present study termed 'self-harm' included both suicide attempts (the majority) and self-harm without the intent of suicide. As we could not distinguish between the two and since underreporting of self-harm and suicide attempts from the Danish registers is a limitation (28), it is possible that clozapine does not have similar effects on the risk of self-harm (without intent of suicide) and the risk of suicide attempt.

Furthermore, the results could be biased due to uncontrolled confounding such as symptom type and severity, non-antipsychotic co-medication and therapeutic treatment, and the inability of the register-based design to distinguish between discontinuation of antipsychotic medication due to medication non-response, intolerance, and non-adherence. Similarly, the register-based definition of treatment resistance is not a perfect proxy because the registers available did not include information on treatment non-response, and our cohort might thus include some individuals being intolerant rather than non-responsive to treatment. Furthermore, we could not take into account the regular contact with the health care system due to clozapine blood monitoring, which could serve as a potential intermediate factor associated with decreased severity in clozapine initiators (12). However, clozapine remained the treatment associated with the lowest rates of death and self-harm in sensitivity analyses compared with long-acting injectable antipsychotics, which similarly require regular contacts with the health-care system. No significant difference were observed between long-acting injectable antipsychotics and other non-clozapine antipsychotics, corroborating the findings of a recent meta-analysis of RCTs (33). Still, clozapine blood monitoring might, at least in part, explain the lower rate of deaths in the first year after clozapine initiation or re-initiation and the higher rate after clozapine discontinuation. Thus, this study explores the overall real-world effect of different antipsychotic treatments rather than exclusively the pharmacological effect of the drugs.

Finally, the design of time-varying treatment and confounders might introduce collider-stratification bias, i.e. due to conditioning on factors affected by both the prior status of the covariate as well as by the prior treatment status. However, alternative methods such as time-varying propensity scores or inverse probability weighting of marginal structural models may not improve results remarkably (34).

Conclusion

The results of the present study indicate that clozapine use is associated with a decreased mortality in line with previous research (10-12). This was, however, only significant when compared with periods of no antipsychotic treatment, probably largely explained by an excess mortality observed after clozapine discontinuation. Furthermore, the results of the present study suggest a protective effect of clozapine in the prevention of self-harm when compared with other antipsychotics, but no effect was found when compared with no use of antipsychotics. It remains unclear whether the protective effect of clozapine in treatment-resistant schizophrenia to prevent self-harm could be partly explained by a potentially harmful effect of alternative treatment strategies with other antipsychotics or confounding by indication. Moreover, the extent to which the observed excess mortality after clozapine discontinuation is caused by side effects from recent clozapine exposure, unobserved factors, or clozapine discontinuation remains to be investigated. This study suggests that clozapine discontinuation needs more attention with a thorough evaluation, care, and monitoring of the patient.

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Table and Figure legends

Table 1 Distributions of clozapine treatment and rates of all-cause death and self-harm by baseline characteristics.

^a Follow-up starts at time point of meeting criteria for treatment-resistant schizophrenia and ends at emigration, death, or June 1, 2013.

^b First episode of self-harm after meeting criteria for treatment-resistant schizophrenia.

^c At least one disease included in the Charlson comorbidity index.

Table 2 Hazard ratios and 95% CIs presented for all-cause mortality for different categorizations of time-dependent antipsychotic (AP) treatment.

^a Adjusted for sex, and time-dependent covariates: age, calendar year, prior episodes of self-harm, substance abuse, comorbid somatic disorders, comorbid psychiatric disorders (other schizophrenia spectrum disorders, depression, personality disorder), living in the capital area, psychiatric hospitalization within the previous year, and cumulative clozapine treatment (0, 0-1, 1-3, 3+ years).

^b Excluding risk time for psychiatric hospitalization after one month allowing the individual to re-enter. N(deaths)=148.

Table 3 Hazard ratios and 95% CI for cause-specific mortality comparing no clozapine treatment to current clozapine treatment after meeting criteria for treatment-resistant schizophrenia. Follow-up restricted to end by December 31, 2011. N=2141.

^a Adjusted for sex, age, calendar year, suicide attempts, substance abuse, somatic comorbidity.

^b Further adjustment for psychiatric hospitalization within previous year.

Table 4 Hazard ratios and 95% CIs presented for self-harm for different categorizations of time-dependent antipsychotic (AP) treatment.

^a Adjusted for sex, and time-dependent covariates: age, calendar year, prior episodes of self-harm, substance abuse, comorbid somatic disorders, comorbid psychiatric disorders (other schizophrenia spectrum disorders, depression, personality disorder), living in the capital area, psychiatric hospitalization within the previous year, and cumulative clozapine treatment (0, 0-1, 1-3, 3+ years).

^b Excluding risk time for psychiatric hospitalization after one month allowing the individual to re-enter. N(self-harm)=576.

Figure 1 All-cause mortality rates estimated in time intervals of current clozapine treatment, no clozapine treatment, and after clozapine discontinuation. Follow-up started at any initiation or discontinuation of a clozapine period, or

at the time of meeting criteria of treatment-resistant schizophrenia (TRS), and ended at any change in clozapine treatment status or end of follow-up. 95% CIs are illustrated by vertical bars.